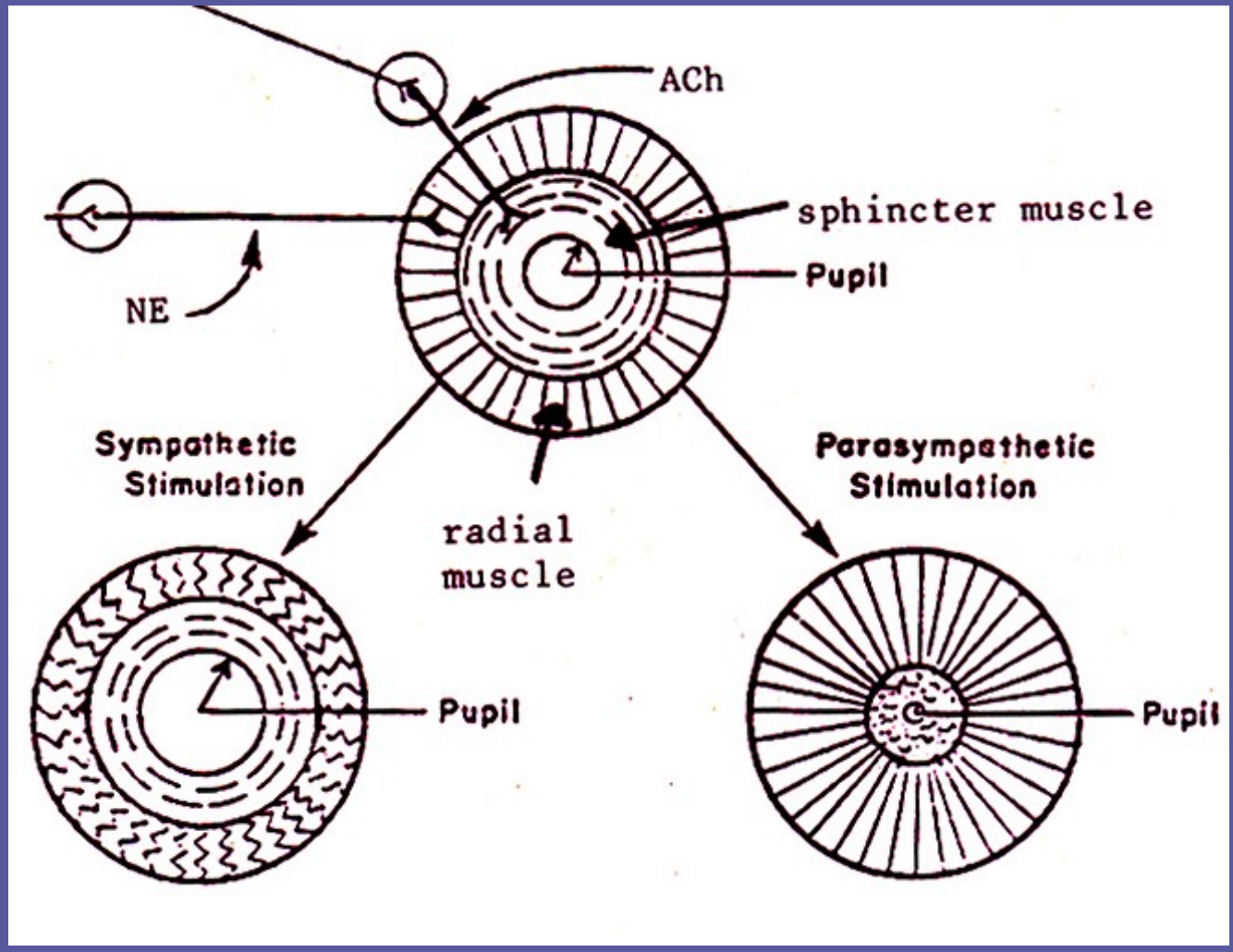
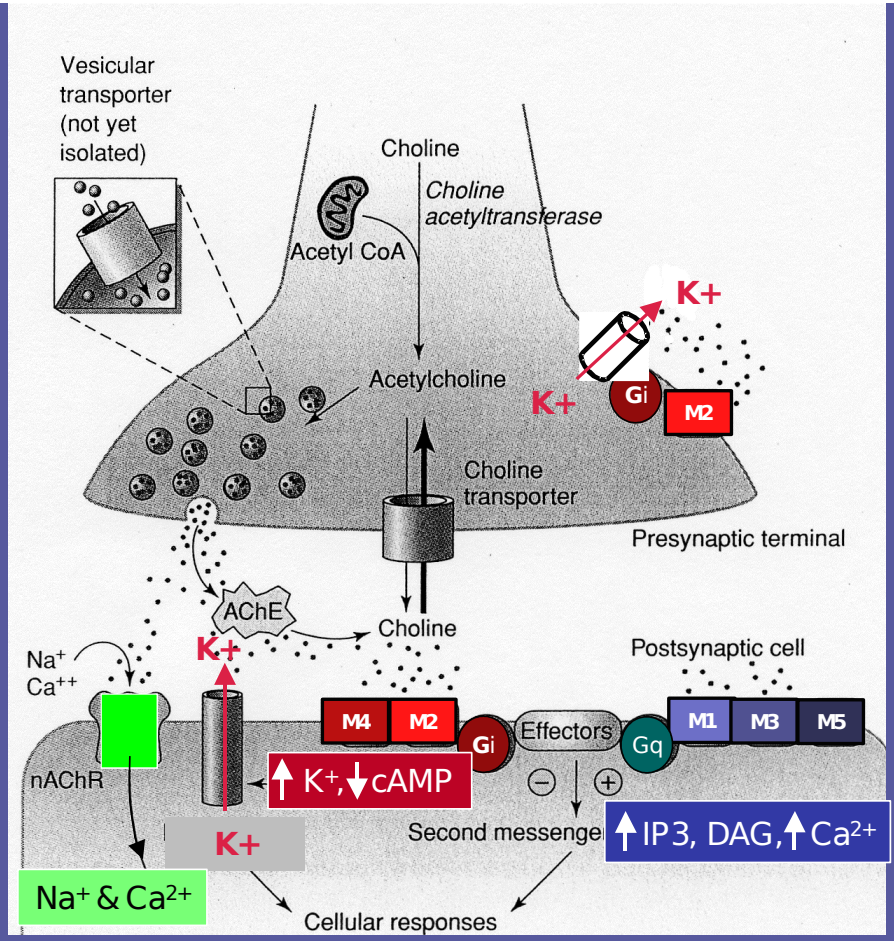

ACh
sphincter muscle
Pupil
NE
Sympathetic
Stimulation
radial
muscle
Parasympathetic
Stimulation
Pupil
Pupil



Nicotinic receptors are ion channels that increase Ca^{2+} and Na^{+} entry into cells.

M1, M3 & M5 muscarinic receptors increase IP_3, and this increases intracellular Ca^{2+}.

M2 & M4 muscarinic receptors inhibit adenylyl cyclase activity and open K^{+} channels to hyperpolarize neurons and close Ca^{2+} channels.

Adrenergic Drugs

- **Adrenergic Neurotransmission, sites of drug action**
- **Agonists etc. (sympathomimetic agents)**
  - **Direct acting**
  - **Indirect acting**
  - **Others**
- **Antagonists etc. (sympatholytic agents)**
  - **Receptor blocking agents**
  - **Agents that interrupt neuronal function**
  - **Centrally acting to reduce sympathetic outflow**

Major uses of Adrenergic Drugs

Disease	Adrenergic Drug
• Asthma	albuterol
• Cardiogenic shock	dopamine
• Rhinitis	phenylephrine
• Hypertension	prazosin
• Angina pectoris	propranolol
• Supraventricular arrhythmias	atenolol
• Benign prostatic hyperplasia	terazosin

Adrenergic Receptors: Intracellular signaling

ADRENERGIC RECEPTOR	G PROTEIN	EXAMPLES OF SOME BIOCHEMICAL EFFECTORS
β_1	G_s	↑ adenylyl cyclase, ↑ L-type Ca^{2+} channels
β_2	G_s	↑ adenylyl cyclase
β_3	G_s	↑ adenylyl cyclase
α_1 Subtypes	G_q	↑ phospholipase C → ↑ IP_3 → ↑ Ca^{2+}
	G_q	↑ phospholipase D
	G_q, G_i/G_o	↑ phospholipase A_2
	G_q	? ↑ Ca^{2+} channels
α_2 Subtypes	$G_{i\ 1,\ 2,\ or\ 3}$	↓ adenylyl cyclase
	G_i ($\beta\gamma$ subunits)	↑ K^+ channels
	G_o	↓ Ca^{2+} channels (L- and N-type)

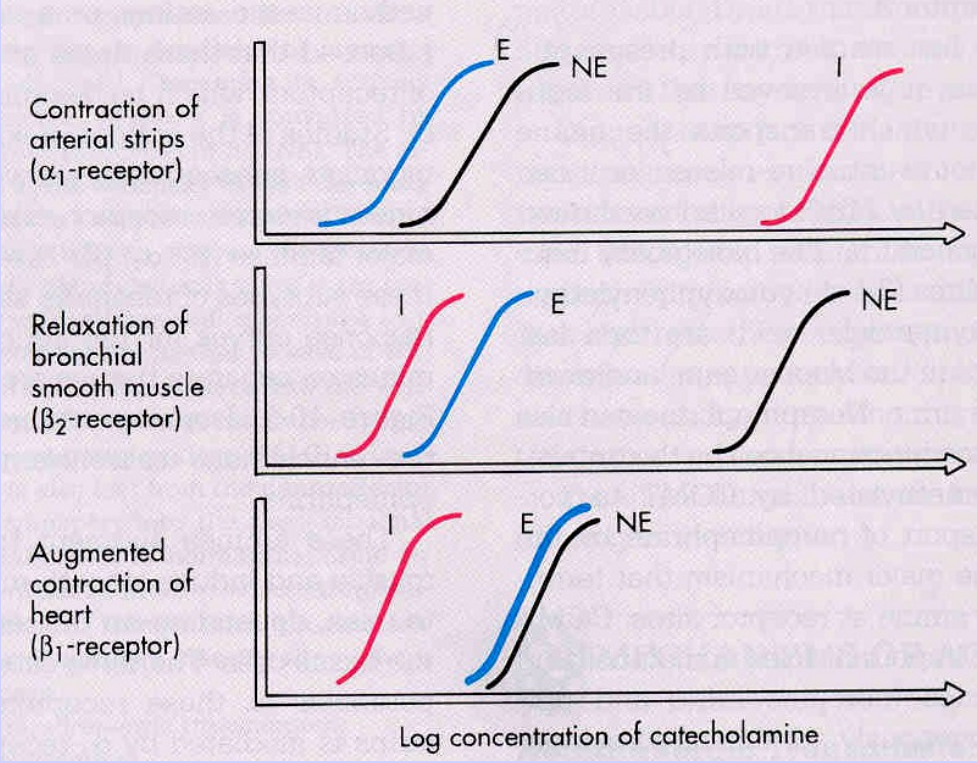
Receptor Affinity of Prototypic Agents

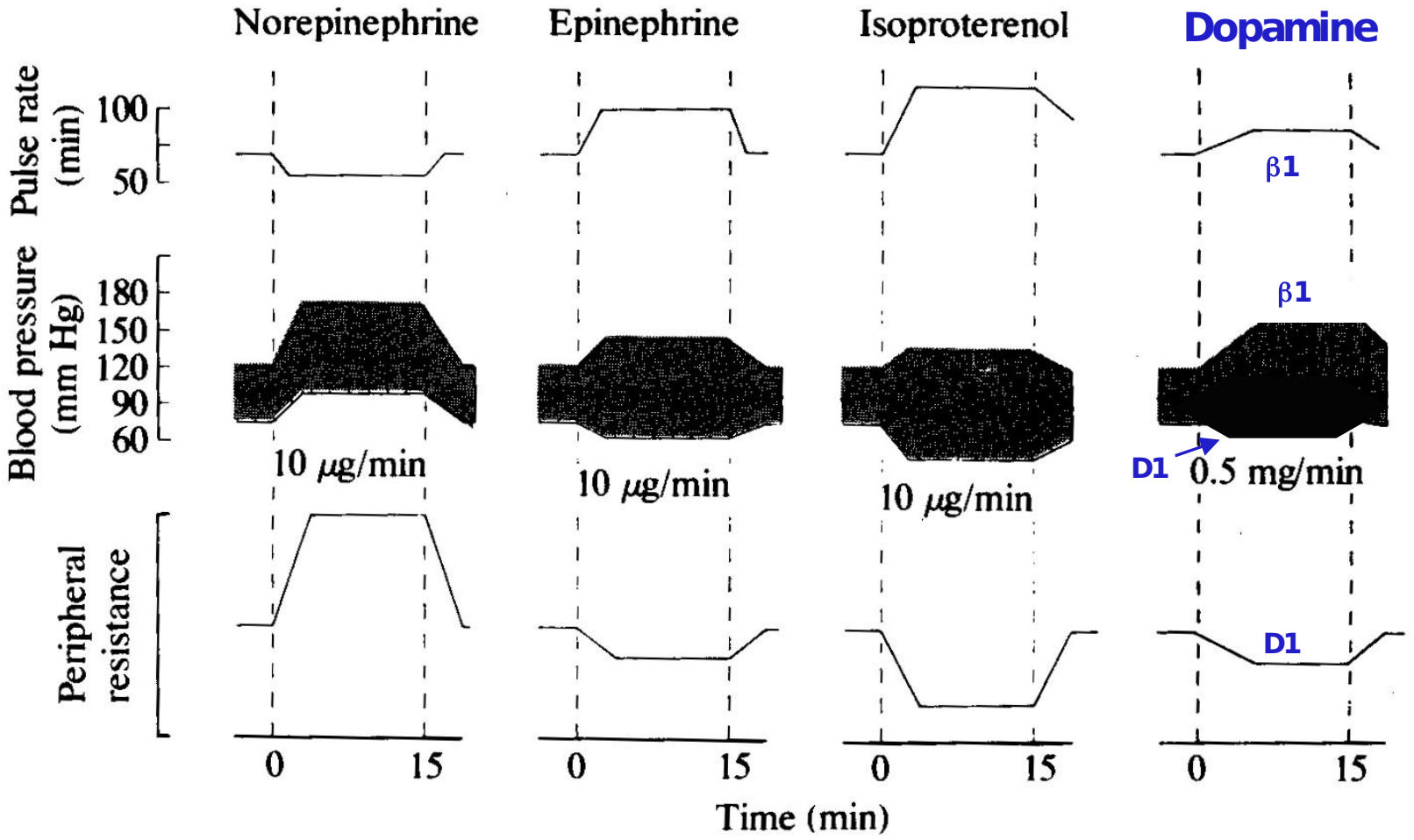
$alpha_1$ & $alpha_2$	$beta_1$	$beta_2$
EPI?NE>>I	I>EPI=NE	I?EPI>>NE

EPI = epinephrine

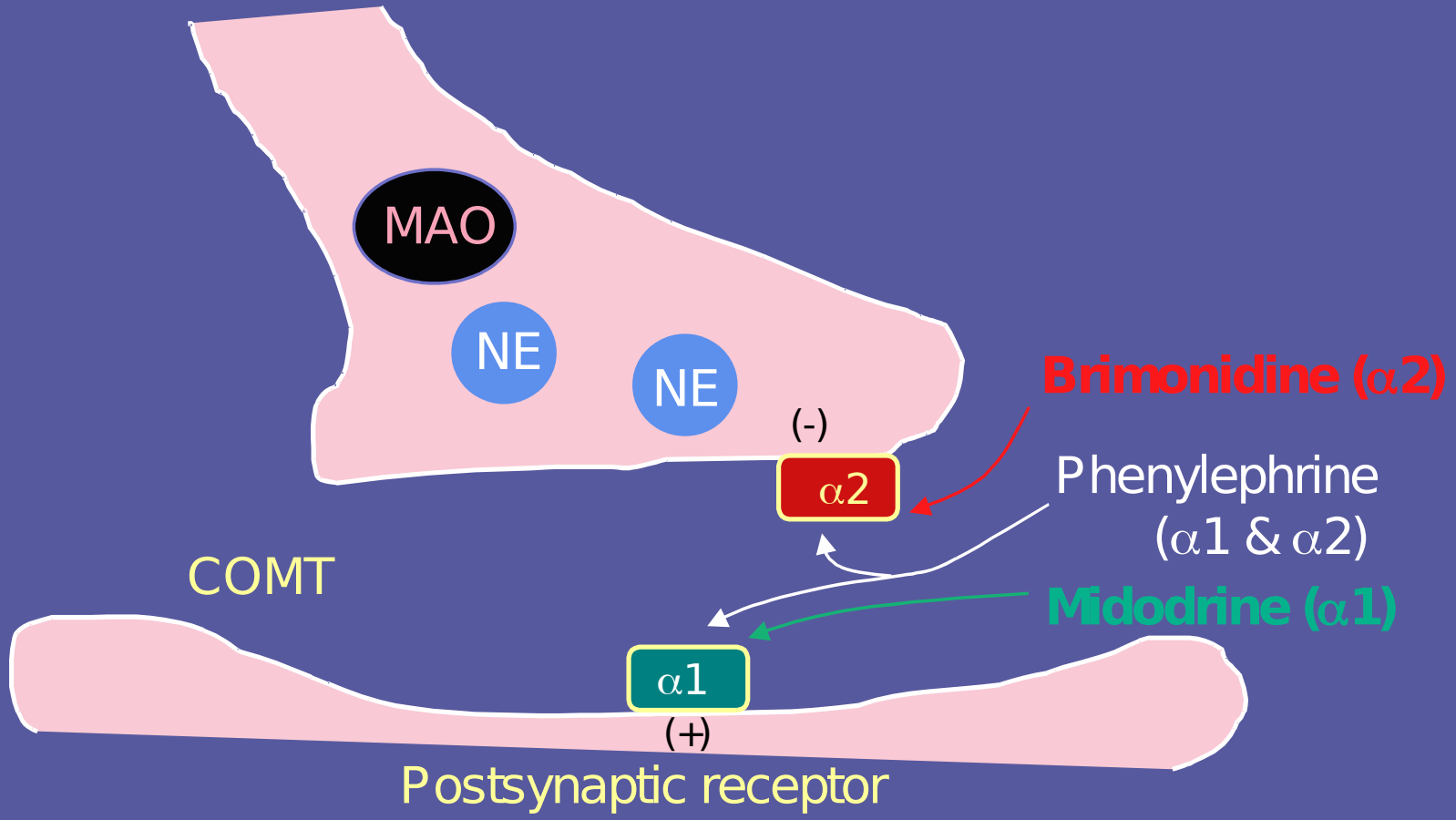
NE = norepinephrine

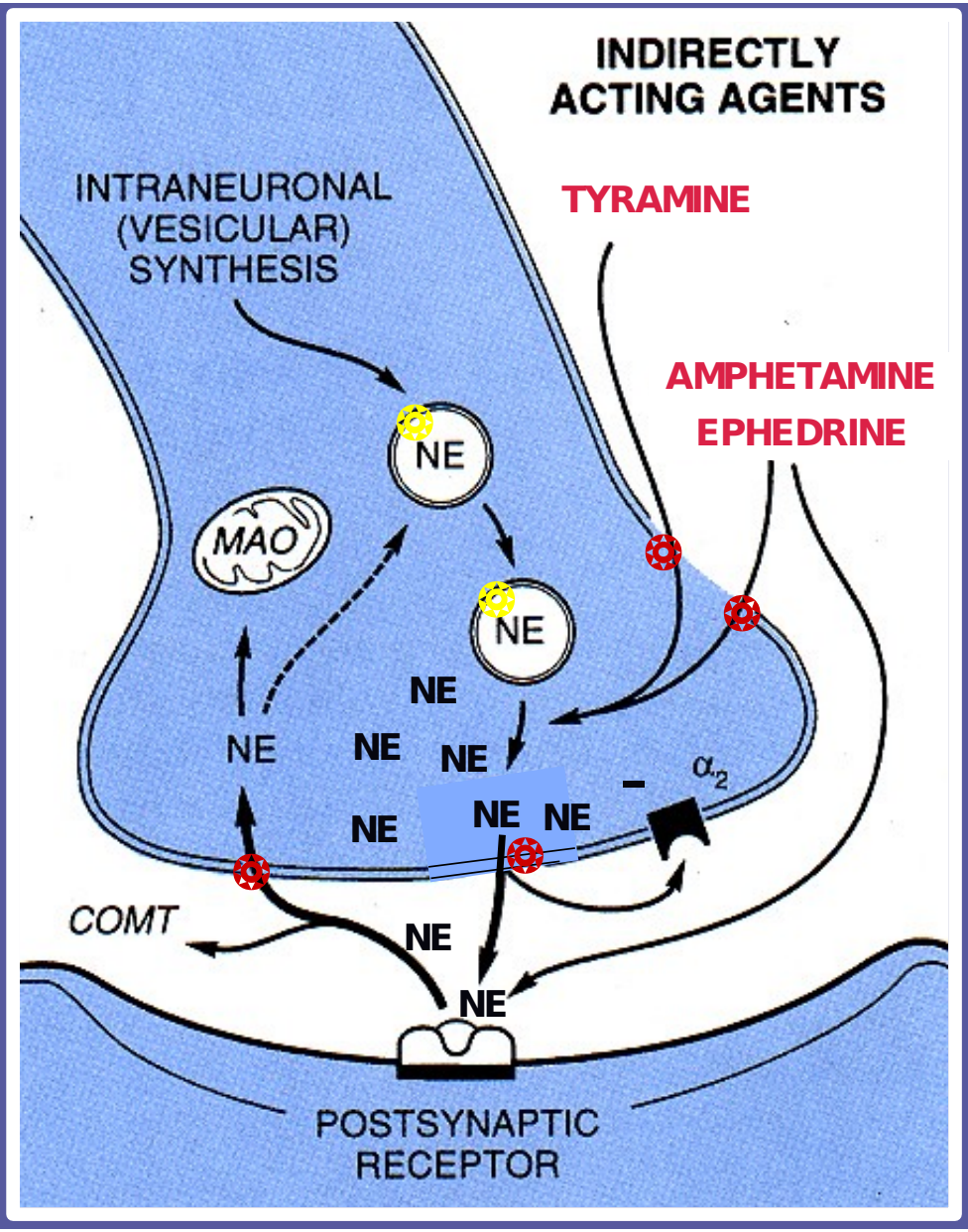
I = isoproterenol

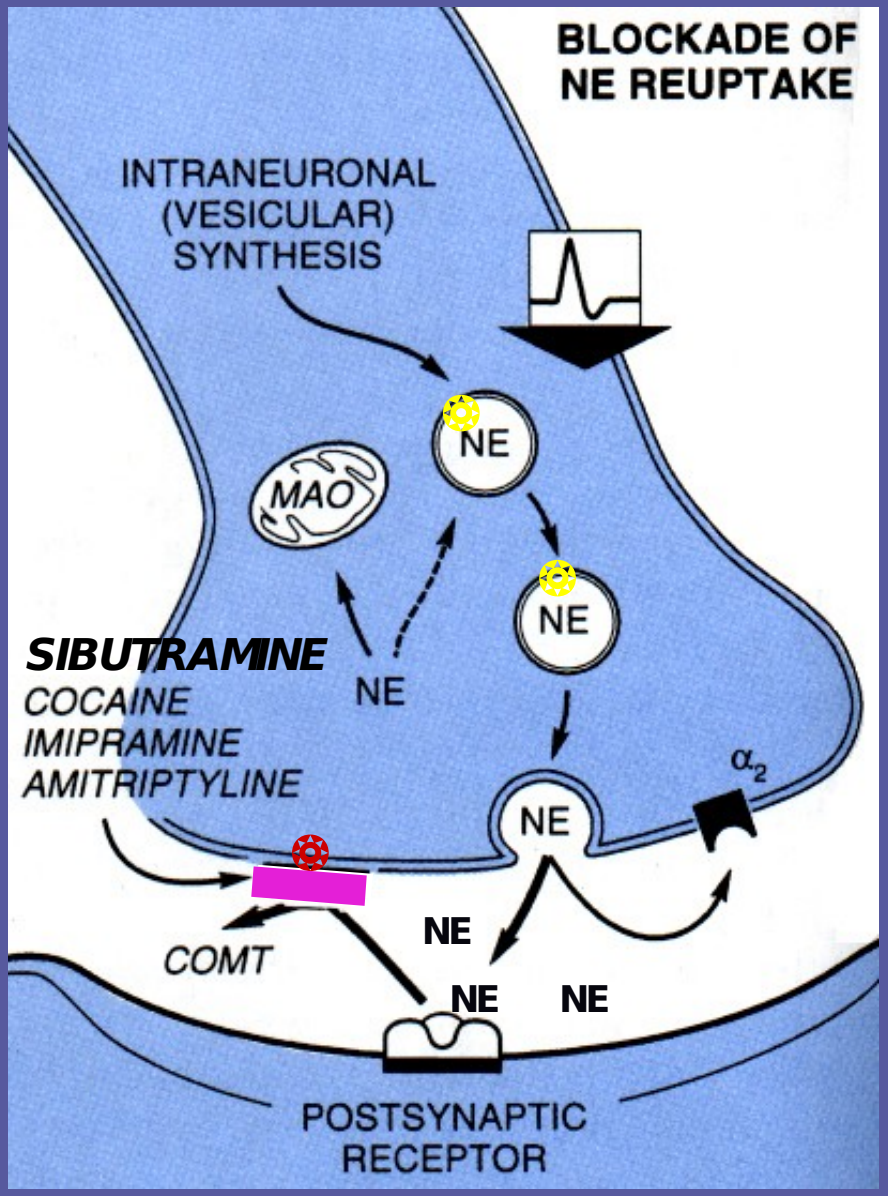


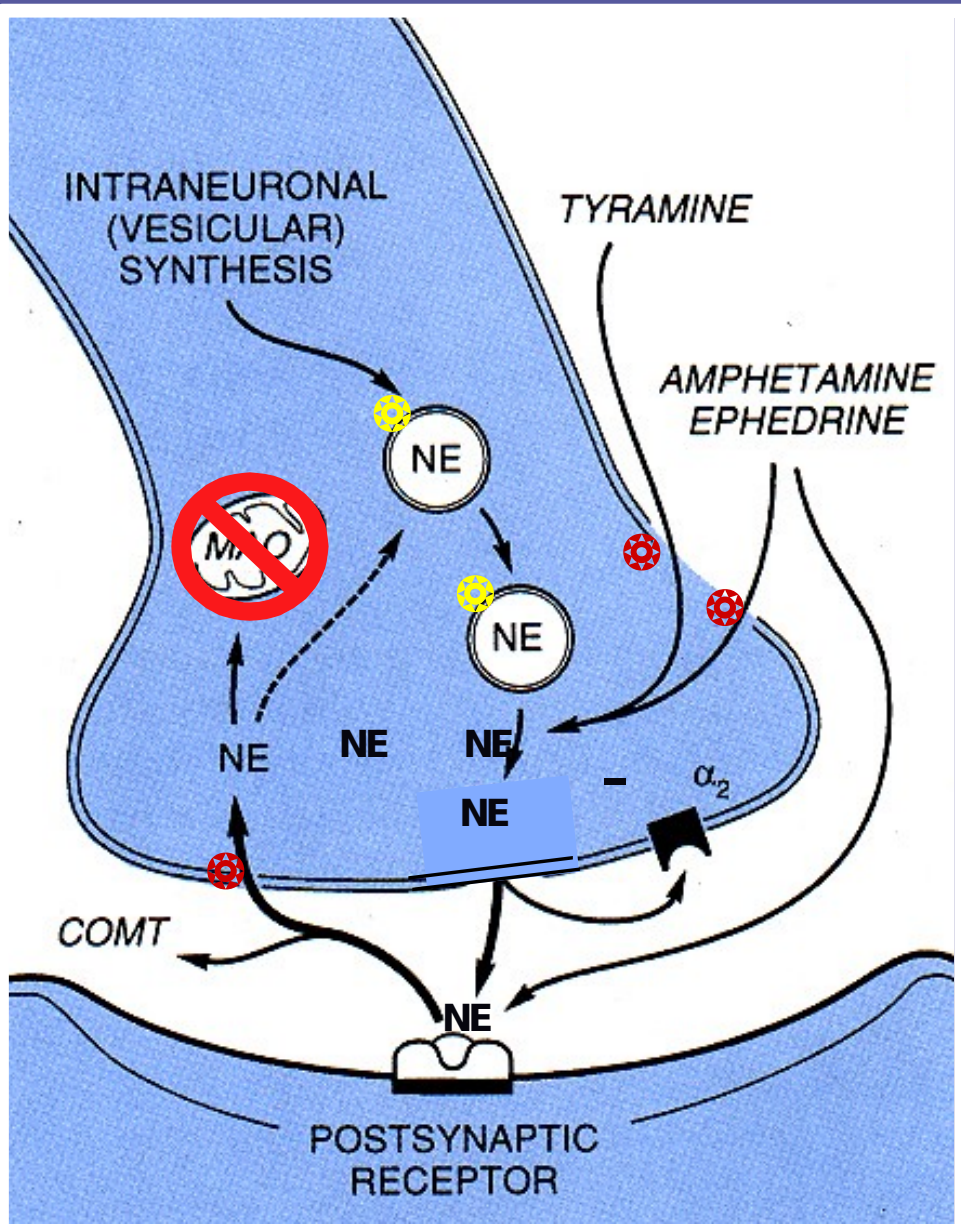

Norepinephrine
Epinephrine
Isoproterenol
Dopamine
Pulse rate (min)
100
50
Blood pressure (mm Hg)
180
150
120
90
60
Peripheral resistance
β1
β1
D1
D1
10 μg/min
10 μg/min
10 μg/min
0.5 mg/min
0
15
0
15
0
15
0
15
Time (min)

Direct acting α adrenergic agonists at sympathetic synapse




INDIRECTLY
ACTING AGENTS
INTRANEURONAL
(VESICULAR)
SYNTHESIS
TYRAMINE
AMPHETAMINE
EPHEDRINE
NE
MAO
NE
NE
NE
NE
NE
NE
NE
NE
α_2
COMT
NE
NE
POSTSYNAPTIC
RECEPTOR

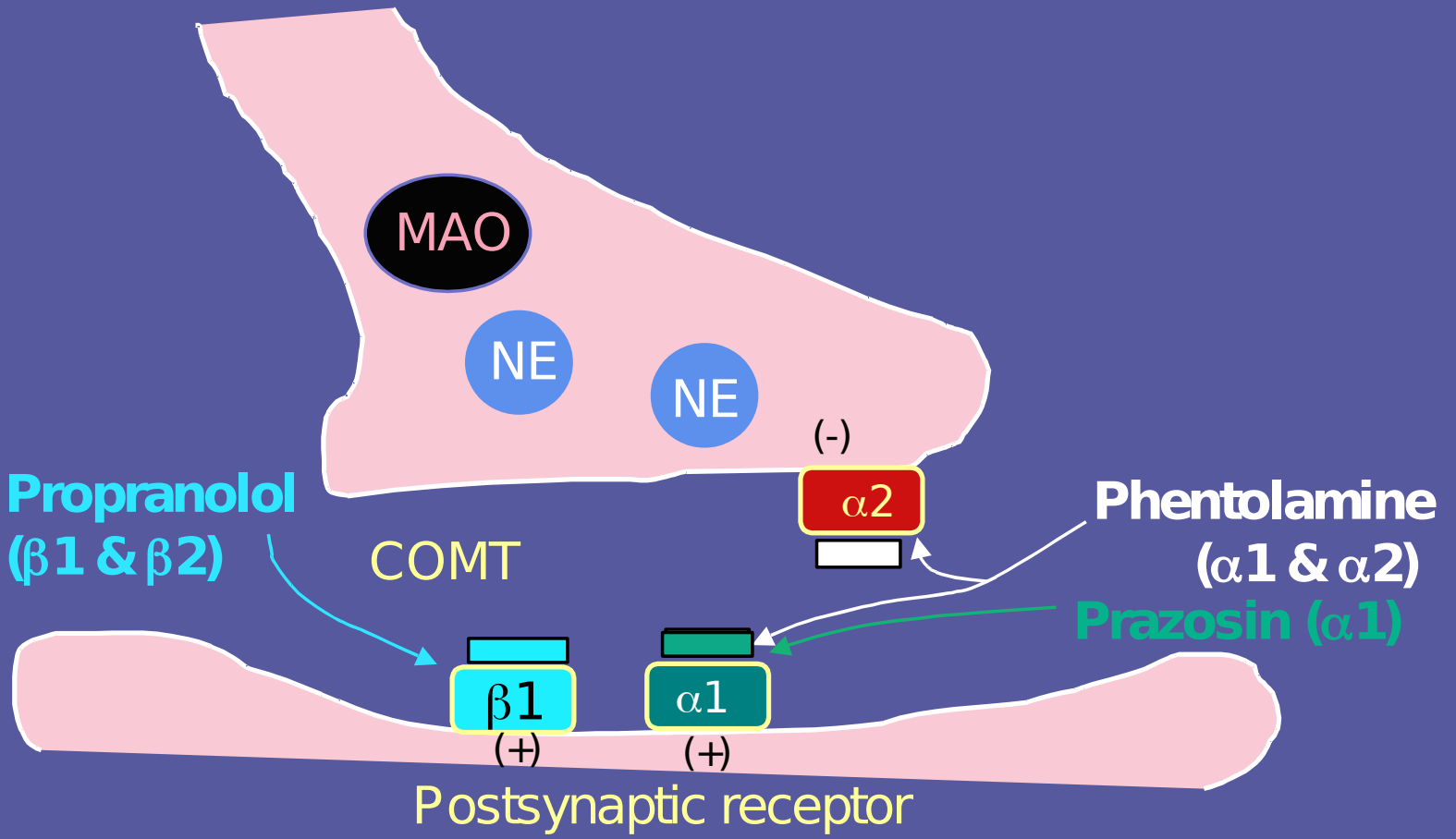

BLOCKADE OF
NE REUPTAKE
INTRANEURONAL
(VESICULAR)
SYNTHESIS
NE
MAO
NE
SIBUTRAMINE
COCAINE
IMIPRAMINE
AMITRIPTYLINE
NE
α_2
NE
NE
COMT
NE
NE
POSTSYNAPTIC
RECEPTOR



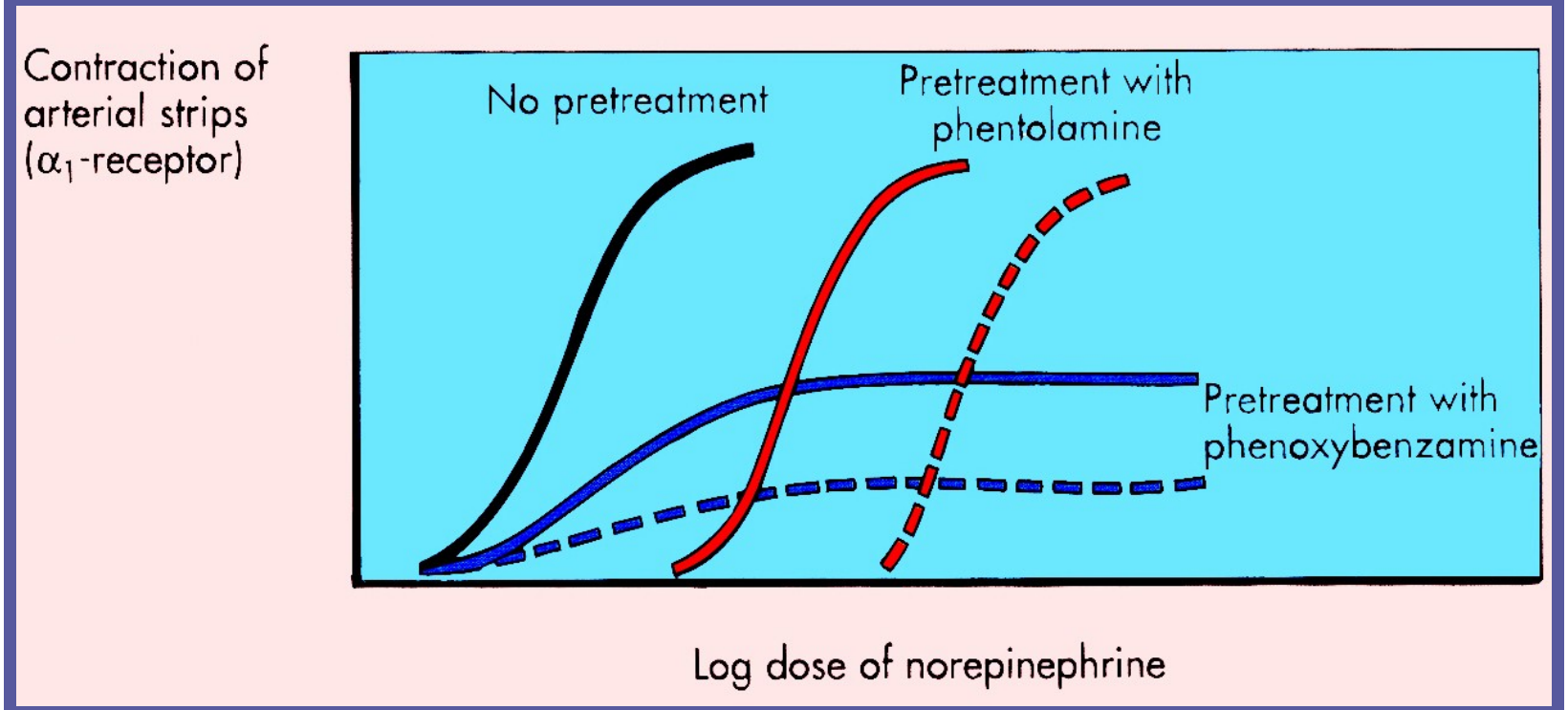
Nonspecific MAO (A&B) inhibitors

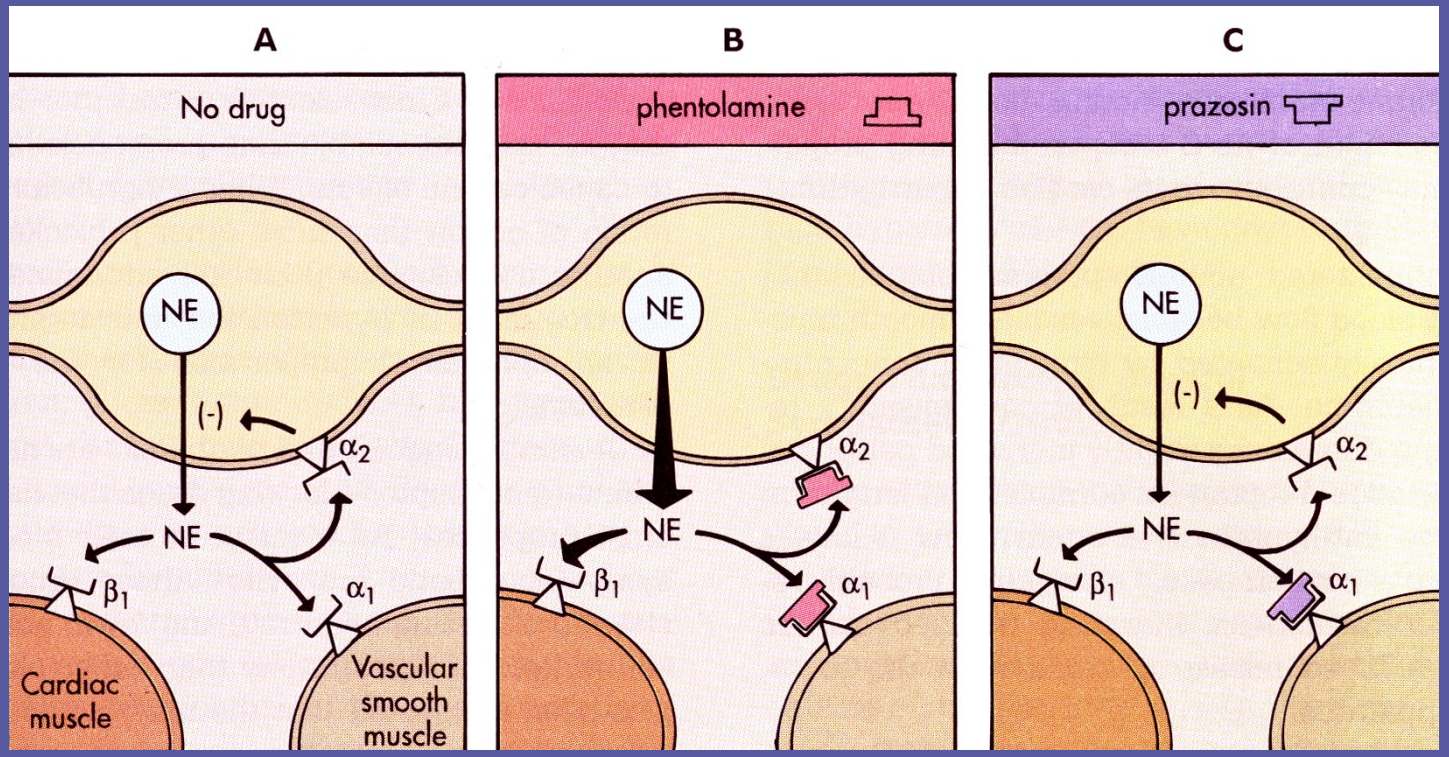
Potential hypertensive crisis with indirect acting agonists

Adrenergic receptor blockade at a sympathetic synapse

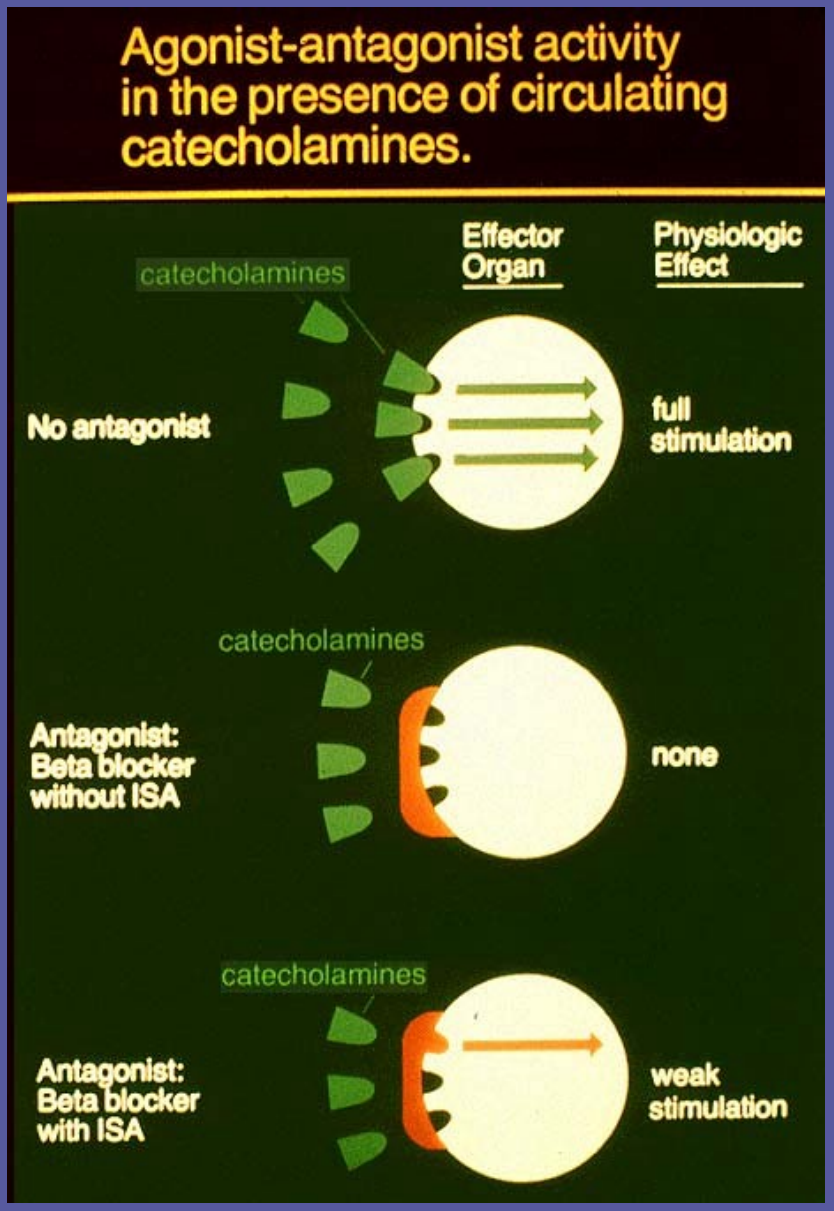


Noncompetitive versus competitive alpha receptor antagonist





Prazosin does NOT block presynaptic $\alpha 2$ receptors,
does not cause increased NE release,
and therefore it does NOT cause tachycardia


Agonist-antagonist activity in the presence of circulating catecholamines.
Effector Organ
Physiologic Effect
catecholamines
No antagonist
full stimulation
catecholamines
Antagonist: Beta blocker without ISA
none
catecholamines
Antagonist: Beta blocker with ISA
weak stimulation

Adrenergic Neuron Blocking Agents

Guanethidine

Bretylium

- prevent action potential-induced release of NE
- gradually replace stored NE